# PCT

## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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|---|---|---|
| (51) International Patent Classification [6] :<br><br>C07C 51/16 | A1 | (11) International Publication Number: **WO 99/52849**<br><br>(43) International Publication Date: 21 October 1999 (21.10.99) |

(21) International Application Number: PCT/US99/07466

(22) International Filing Date: 5 April 1999 (05.04.99)

(30) Priority Data:
60/081,202    9 April 1998 (09.04.98)    US
9810188.4    13 May 1998 (13.05.98)    GB

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(81) Designated States: AE, AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TJ, TM, TR, TT, UA, US, UZ, VN, YU, ZA, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
*With international search report.*

(54) Title: OXIDATION PROCESS USING TEMPO

(57) Abstract

The present invention relates to the oxidation of a primary alcohol of Formula (II) to the carboxylic acid of Formula (I): $R^1CH_2OH \rightarrow R^1CO_2H$.

# TITLE OF THE INVENTION
## OXIDATION PROCESS USING TEMPO

## BACKGROUND OF THE INVENTION

5          Oxidation is one of the most fundamental transformations in organic synthesis and there are numerous methods reported in the literature. (Hudlicky, M. "Oxidations In Organic Chemistry", ACS Monograph No. 186 American Chemical Society Washington D.C. (1990).) However, relatively few methods exist for the oxidation of 10   primary alcohols to the corresponding carboxylic acids. The most commonly used ones are $CrO_3/H_2SO_4$ (Bowden; Heilbron; Jones; Weedon *J. Chem. Soc.*, **1946**, 39; Bowers; H.; Jones; L. *J. Chem. Soc.*, **1953**, 2548; Millar, J. G.; Oehlschlager, A. C.; Wong, J. W. *J. Org. Chem.* **1983**, *48*, 4404.), $RuCl_3/H_5IO_6$ (Carlsen, P. H. J.; Katsuki, T.; Martin V. S.; 15   Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936.) and TEMPO/NaClO (Nooy, A. E. J. de; Besemer, A. C.; Bekkum, H. v. *Synthesis*, **1996**, 1153.; Anelli, P. L.; Biffi, C.; Montanari, F.; Quici, S. *J. Org. Chem.* **1987**, *52*, 2559.; Miyazawa, T.; Endo, T.; Shiihashi, S.; Okawara, M. *J. Org. Chem.* **1985**, *50*, 1332). A two-step process involving Swern oxidation 20   (Mancuso, A. J.; Huang, S-L., Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.; Mancuso, A. J.; Brownfan, D. S.; Swern, D. *J. Org. Chem.* **1979**, *44*, 4148.; Ireland, R.; Norbeck, D. *J. Org. Chem.* **1985**, *50*, 2198.) followed by oxidation of the resulting aldehyde with $NaClO_2$ (Lindgren, B. O.; Nilsson, T. *Acta Chem. Scand.* **1973**, *27*, 888.; Dalcanale, E.; Montanari, 25   F. *J. Org. Chem.* **1986**, *51*, 567) is another option. All of these procedures have some limitations and disadvantages and new methods for the oxidation of primary alcohols to the carboxylic acids are still desired. (Schroder, M.; Griffith, W. P. *J. Chem. Soc. Chem. Comm.* **1979**, 58.; and Paquette, L. A.; Dressel, J.; Pansegrau, P. D. *Tetrahedron Lett.* 30   **1987**, *28*, 4965.)

          The present invention relates to an oxidation using sodium chlorite in the presence of a catalytic amount of TEMPO and sodium hypochlorite which converts a primary alcohol to a carboxylic acid. This oxidation method avoids the disposal issues associated with running a 35   Jones oxidation ($CrO_3/H_2SO_4$) reaction, as well as reducing the

epimerization of any $\alpha$-chiral centers and is a one step procedure. For substrates prone to chlorination with the TEMPO-NaClO protocol, the present invention reduces this problem.

5    SUMMARY OF THE INVENTION
         The present invention discloses a process for preparing a compound of Formula I:

$$R^1\text{-}CO_2H$$

I
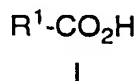
wherein:

10       $R^1$ is:
         a)    H,
         b)    $C_1$-$C_8$ alkyl,
         c)    $C_2$-$C_8$ alkynyl,
         d)    $C_3$-$C_7$ cycloalkyl,
15       e)    aryl,
         f)    heteroaryl, or
         g)    heterocyclyl;

         $C_1$-$C_8$ alkoxy, $C_1$-$C_8$ alkyl, $C_2$-$C_8$ alkynyl, or $C_3$-$C_8$ cycloalkyl, are
             unsubstituted or substituted with one, two or three
20           substituents selected from the group consisting of: OH,
             $CO_2R^4$, Br, Cl, F, I, $CF_3$, $C_1$-$C_8$ alkoxy, $C_3$-$C_8$ cycloalkyl,
             aryl, heteroaryl, heterocyclyl, and $CO(CH_2)_nCH_3$,

         aryl is defined as phenyl or naphthyl , which is unsubstituted or
             substituted with one, two or three substituents selected from
25           the group consisting of: OH, $CO_2R^4$, Br, Cl, F, I, $CF_3$, $C_1$-$C_8$
             alkoxy, $C_1$-$C_8$ alkyl, $C_2$-$C_8$ alkynyl, or $C_3$-$C_8$ cycloalkyl,
             $CO(CH_2)_nCH_3$, or when aryl is substituted on adjacent
             carbons they can form a 5- or 6-membered fused ring
             having one, two or three heteroatoms selected from O, N,
30           and S, this ring is unsubstituted or substituted on carbon or
             nitrogen with one, two or three substituents selected from

the group consisting of: OH, $CO_2R^4$, Br, Cl, F, I, $CF_3$, $C_1$-$C_8$ alkoxy, $C_1$-$C_8$ alkyl, $C_2$-$C_8$ alkenyl, $C_2$-$C_8$ alkynyl, $C_3$-$C_8$ cycloalkyl, and $CO(CH_2)_nCH_3$;

heteroaryl is defined as a 5- or 6-membered aromatic ring containing 1, 2 or 3 heteroatoms selected from O, N and S , which is unsubstituted or substituted with one, two or three substituents selected from the group consisting of: OH, $CO_2R^4$, Br, Cl, F, I, $CF_3$, $C_1$-$C_8$ alkoxy, $C_1$-$C_8$ alkyl, $C_2$-$C_8$ alkynyl, $C_3$-$C_8$ cycloalkyl, $CO(CH_2)_nCH_3$, and additionally the 5- or 6-membered aromatic ring can be benzofused and unsubstituted or substituted with one, two or three substituents as described above;

heterocyclyl is defined as a 5- or 6-membered, non-aromatic ring containing 1, 2 or 3 heteroatoms selected from O, N and S , which may contain one or two double bonds and which is unsubstituted or substituted with one, two or three substituents selected from the group consisting of: OH, $CO_2R^4$, Br, Cl, F, I, $CF_3$, $C_1$-$C_8$ alkoxy, $C_1$-$C_8$ alkyl, $C_2$-$C_8$ alkynyl, or $C_3$-$C_8$ cycloalkyl, $CO(CH_2)_nCH_3$, and additionally the 5- or 6-membered ring can be benzofused and unsubstituted or substituted with one, two or three substituents as described above;
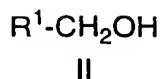
n is: 0 to 5;

t is: 0, 1 or 2;

$R^4$ is: H, or $C_1$-$C_8$ alkyl; or

comprising the following steps:
1)      adding to a compound of Formula II in a solvent,

$$R^1\text{-}CH_2OH$$

$$II$$

a solution of phosphate buffer to maintain a pH of about 4.0 to about 8.0;

5      2)      maintaining the phosphate-buffered biphasic mixture of the compound of Formula II at about 0°C to about 50°C;

       3)      adding a catalytic amount of TEMPO to the mixture; and

10     4)      charging the TEMPO/phosphate-buffered biphasic mixture with a solution of sodium chlorite and a catalytic amount of sodium hypochlorite to oxidize to the compound of Formula I.

## DETAILED DESCRIPTION OF THE INVENTION

15             The present invention discloses a process for preparing a compound of Formula I:

$$R^1\text{-}CO_2H$$

$$I$$
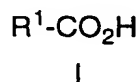
wherein:
       $R^1$ is:
20     a)      H,
       b)      $C_1$-$C_8$ alkyl,
       c)      $C_2$-$C_8$ alkynyl,
       d)      $C_3$-$C_7$ cycloalkyl,
       e)      aryl,
25     f)      heteroaryl, or
       g)      heterocyclyl;

$C_1$-$C_8$ alkoxy, $C_1$-$C_8$ alkyl, $C_2$-$C_8$ alkynyl, or $C_3$-$C_8$ cycloalkyl, are unsubstituted or substituted with one, two or three substituents selected from the group consisting of: OH,

$CO_2R^4$, Br, Cl, F, I, $CF_3$, $C_1$-$C_8$ alkoxy, $C_3$-$C_8$ cycloalkyl, aryl, heteroaryl, heterocyclyl, and $CO(CH_2)_nCH_3$,

aryl is defined as phenyl or naphthyl, which is unsubstituted or substituted with one, two or three substituents selected from the group consisting of: OH, $CO_2R^4$, Br, Cl, F, I, $CF_3$, $C_1$-$C_8$ alkoxy, $C_1$-$C_8$ alkyl, $C_2$-$C_8$ alkynyl, or $C_3$-$C_8$ cycloalkyl, $CO(CH_2)_nCH_3$, or when aryl is substituted on adjacent carbons they can form a 5- or 6-membered fused ring having one, two or three heteroatoms selected from O, N, and S, this ring is unsubstituted or substituted on carbon or nitrogen with one, two or three substituents selected from the group consisting of: OH, $CO_2R^4$, Br, Cl, F, I, $CF_3$, $C_1$-$C_8$ alkoxy, $C_1$-$C_8$ alkyl, $C_2$-$C_8$ alkenyl, $C_2$-$C_8$ alkynyl, $C_3$-$C_8$ cycloalkyl, and $CO(CH_2)_nCH_3$;

heteroaryl is defined as a 5- or 6-membered aromatic ring containing 1, 2 or 3 heteroatoms selected from O, N and S, which is unsubstituted or substituted with one, two or three substituents selected from the group consisting of: OH, $CO_2R^4$, Br, Cl, F, I, $CF_3$, $C_1$-$C_8$ alkoxy, $C_1$-$C_8$ alkyl, $C_2$-$C_8$ alkynyl, $C_3$-$C_8$ cycloalkyl, $CO(CH_2)_nCH_3$, and additionally the 5- or 6-membered aromatic ring can be benzofused and unsubstituted or substituted with one, two or three substituents as described above;

heterocyclyl is defined as a 5- or 6-membered, non-aromatic ring containing 1, 2 or 3 heteroatoms selected from O, N and S, which may contain one or two double bonds and which is unsubstituted or substituted with one, two or three substituents selected from the group consisting of: OH, $CO_2R^4$, Br, Cl, F, I, $CF_3$, $C_1$-$C_8$ alkoxy, $C_1$-$C_8$ alkyl, $C_2$-$C_8$ alkynyl, $C_3$-$C_8$ cycloalkyl, $CO(CH_2)_nCH_3$, and additionally the 5- or 6-membered ring can be benzofused and

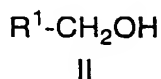unsubstituted or substituted with one, two or three
substituents as described above;

n is: 0 to 5;

t is: 0, 1 or 2;

$R^4$ is: H, or $C_1$-$C_8$ alkyl; or

comprising the following steps:

    1)     adding to a compound of Formula II in a solvent,

$$R^1\text{-}CH_2OH$$
$$II$$

        a solution of phosphate buffer to maintain a pH of about 4.0
        to about 8.0;

    2)     maintaining the phosphate-buffered biphasic mixture of the
        compound of Formula II at about 0°C to about 50°C;

    3)     adding a catalytic amount of TEMPO to the mixture; and

    4)     charging the TEMPO/phosphate-buffered biphasic mixture
        with a solution of sodium chlorite and a catalytic amount of
        sodium hypochlorite to oxidize to the compound of Formula I.

        The process as recited above, wherein the solvent is selected
from the group consisting of: acetonitrile, tetrahydrofuran, acetone,
tertiary $C_4$-$C_8$-alcohol, diethyl ether, DME (dimethyl ether), diglyme,
triglyme, MTBE (methyl t-butyl ether), toluene, benzene, hexane,
pentane, dioxane, dichloromethane, chloroform, carbon tetrachloride,
or a mixture of said solvents.

        The process as recited above, wherein the phosphate buffer
comprises an aqueous mixture of NaOH, KOH, $NaH_2PO_4$, $KH_2PO_4$,

$Na_2HPO_4$, and $K_2HPO_4$, sufficient to maintain a pH of about 4.0 to about 8.0, and preferably a pH of about 6.5 to about 7.0.

The process as recited above, wherein TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy, free radical) is used in about 1.0 to about 10.0 mole percent, preferably about 5.0 to about 7.0 mole percent.

The process as recited above, wherein sodium chlorite is used in about 1.0 to about 3.0 equivalents, and preferably about 2.0 equivalents relative to the compound of Formula II.

The process as recited above, wherein sodium hypochlorite is used in about 1.0 to about 7.0 mole percent, preferably about 2.0 to about 5.0 mole percent.

The process as recited above, wherein the reaction temperature is about 0°C to about 50°C, and preferably about 35°C to about 40°C.

The process as recited above, wherein the reaction time is up to about 24 hours, and preferably between about 2 and about 4 hours.


It is further understood that the substituents recited above would include the definitions recited below.

The alkyl substituents recited above denote straight and branched chain hydrocarbons of the length specified such as methyl, ethyl, isopropyl, isobutyl, tert-butyl, neopentyl, isopentyl, etc.

Cycloalkyl denotes rings composed of 3 to 8 methylene groups, each of which may be substituted or unsubstituted with other hydrocarbon substituents, and include for example cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and 4-methylcyclohexyl.

The alkoxy substituent represents an alkyl group as described above attached through an oxygen bridge.

The aryl substituent represents phenyl and 1-naphthyl or 2-naphthyl, including aryls substituted with a 5- or 6-membered fused ring, such as an unsubstituted and substituted methylenedioxy, oxazolyl, imidazolyl, or thiazolyl ring.

The heteroaryl substituent represents a carbazolyl, furanyl, thienyl, pyrrolyl, isothiazolyl, imidazolyl, isoxazolyl, thiazolyl, oxazolyl, pyrazolyl, pyrazinyl, pyridyl, pyrimidyl, purinyl.

The heterocyclyl substituent represents, oxazolidinyl, thiazolidinyl, thiazolidinyl, oxadiazolyl, or thiadiazolyl.

Each of the above substituents (alkyl, alkynyl, alkoxy, cycloalkyl, aryl, heteroaryl, and heterocyclyl) can be either

5    unsubstituted or substituted as defined within the description.

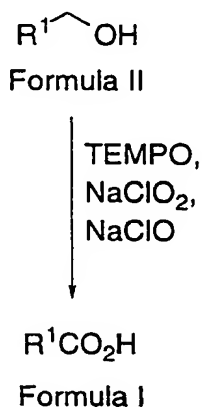Recently, in an attempt to oxidize primary alcohols, such as **1m**:
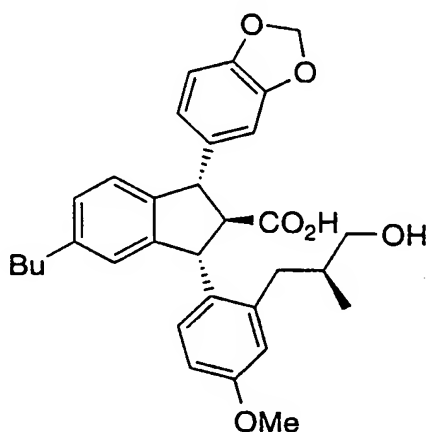


**1m**

to the corresponding carboxylic acid, we found that $RuCl_3/H_5IO_6$ protocol offered low yield of the desired products. See Carlsen, P. H. et al. *J. Org.*

10    *Chem.* **1981**, *46*, 3936. It was probably due to the destruction of electron rich aromatic ring. TEMPO catalyzed oxidation with bleach also gave low yield due to significant chlorination of the aromatic rings. See A. E. J. de Nooy, et al. *Synthesis*, **1996**, 1153.; P. L. Anelli, et al. S. *J. Org. Chem.* **1987**, *52*, 2559. and T. Miyazawa, et al. *J. Org. Chem.* **1985**, *50*, 1332. The synthesis

15    of **1m** is decribed in Merck Case No. 20127PV, entitled "Oxidation Process Using TEMPO" which is being filed simultaneously with this application.

In order to eliminate the chlorination problem, a few other oxidants ($H_2O_2$, $AcO_2H$, $t$-$BuO_2H$ etc.) were examined, but no satisfactory

20    results was obtained. Finally, when sodium chlorite ($NaClO_2$) was used as the oxidant, the product were obtained in 70-90% yield. The reaction appeared to be very slow (1-2%/hour) but generally went to completion overnight (~20 hours). More careful monitoring of the reaction indicated

that it was self accelerating process e.g. the conversion was less than 5% after one hour but reached ~90% in only 6 hours. Apparently, some more active species was generated as the reaction progress. Sodium hypochlorite (NaClO, bleach) was believed to be the most likely

5  candidate. Indeed, when 10mol% of bleach was added to the reaction mixture, the reaction was accelerate dramatically. It reached >50% conversion in one hour and finished in approximately three hours.

**SCHEME 1**

$$R^1 \frown OH$$

Formula II

$$\downarrow \quad \begin{array}{l} \text{TEMPO,} \\ \text{NaClO}_2, \\ \text{NaClO} \end{array}$$

$$R^1CO_2H$$

10                               Formula I

The reaction was then optimized regard to further reduce the chlorination and enhance the safety for scale up. The reaction was faster at lower pH, but it was accompanied by increased chlorination. It was slower at lower temperature as expected, but surprisingly, the

15  chlorination level appeared to be slightly elevated. Increasing the amount of TEMPO and bleach increased the reaction rate, but the TEMPO/NaClO ratio should be >2 to reduce the chances of chlorination. The bleach was added slowly and simultaneously with $NaClO_2$ to the batch at 35 °C to prevent build up of the oxidant and the risk of a run

20  away reaction. It should be noted that mixing of bleach and $NaClO_2$ prior to the addition is not advised since some toxic and potentially explosive chlorine dioxide ($ClO_2$) may be generated.

Next, a number of primary alcohols were oxidized to the carboxylic acids and the results are summarized in Table 1. In general,

25  the reaction were very smooth and the yield were excellent (85-100%).

Chiral alcohols **1g**, **1j**, and **1k** were oxidized to the corresponding carboxylic acid without any racemization of the labile chiral centers.

Mostly notably, for substrates prone to chlorination (**1c-1h**), our new procedure gave much better yields.  The most dramatic

5     demonstration of the superiority of our new procedure was revealed in entry 5.  When **1e** was treated with NaClO and catalytic TEMPO, the desired product was obtained in less than 5% yield.  One of the major side product was isolated and identified to be the chlorinated compound **4,**
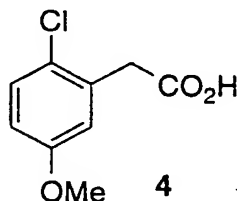


10    based on NMR studies.   On the other hand, our TEMPO/NaClO$_2$ protocol offered essentially quantitative yield of **2e**.

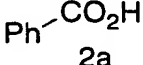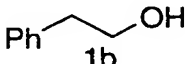## Table 1: TEMPO Catalyzed Oxidation of Primary Alcohols to Carboxylic Acids
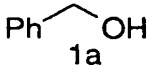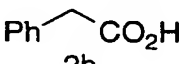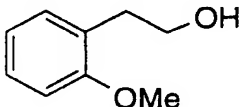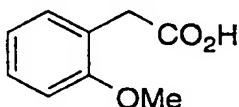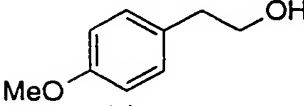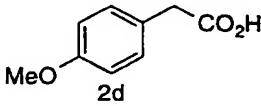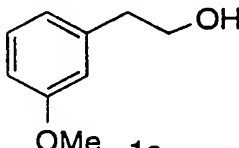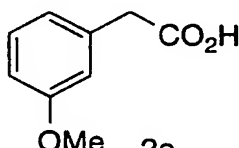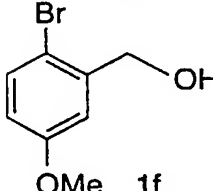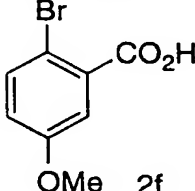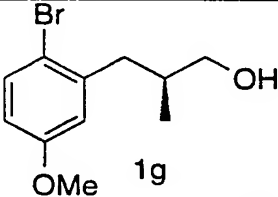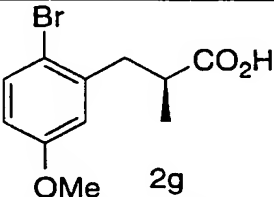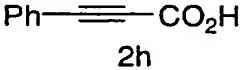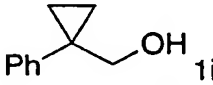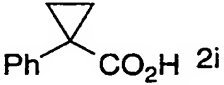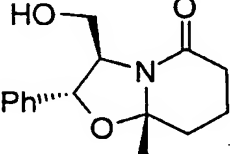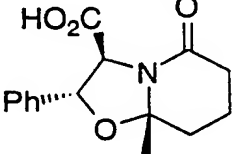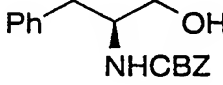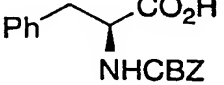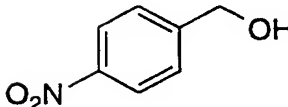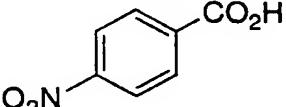
| Substrate | Product | Yield (NaClO$_2$) | Yield (NaClO) |
|---|---|---|---|
| Ph⁀OH **1a** | Ph⁀CO$_2$H **2a** | 98% | - |
| Ph⁀⁀OH **1b** | Ph⁀CO$_2$H **2b** | 100% | - |
| 2-OMe phenethyl alcohol **1c** | 2-OMe phenylacetic acid CO$_2$H **2c** | 99% | 65% |
| 4-MeO phenethyl alcohol **1d** | 4-MeO phenylacetic acid CO$_2$H **2d** | 100% | 86% |
| 3-OMe phenethyl alcohol **1e** | 3-OMe phenylacetic acid CO$_2$H **2e** | 96% | <5% |
| Br, 5-OMe benzyl alcohol **1f** | Br, CO$_2$H 5-OMe **2f** | 96% | 80% |

## Table 1: (Cont.) TEMPO Catalyzed Oxidation of Primary Alcohols to Carboxylic Acids

| Substrate | Product | Yield (NaClO$_2$) | Yield (NaClO) |
|---|---|---|---|
| 1g | 2g | 92% | 60% |
| 1h | 2h | 90% | 20% |
| 1i | 2i | 95% | - |
| 1j | 2j | 95% | - |
| 1k | 2k | 85% | - |
| 1l | 2l | 100% | - |

In conclusion, an efficient and environmentally benign procedure for the oxidation of primary alcohols to the carboxylic acids has been developed. In this procedure, NaClO$_2$ is used as the stoichiometric oxidant in the presence of catalytic amount of TEMPO

and bleach (NaClO).  Most primary alcohols were oxidized in essentially
quantitative yield.  Compared with TEMPO/NaClO/CH₂Cl₂ protocol, the
amount of chlorination of  electron rich aromatic rings in the substrates
were dramatically reduced and the yield and purity of the products            —
5    improved.  Additionally, no chlorinated solvent is used.

The instant invention can be understood further by the
following examples, which do not constitute a limitation of the invention.
**General:**

All substrates and reagents were obtained
10    commercially, except **1g** (See Examples 2-5 decribing the preparation of
this primary alcohol) and used without purification.  ¹H and ¹³C NMR
spectra were recorded at 250 and 62.5 MHz respectively.  The products
were identified by comparing their NMR spectra with those of
commercial materials except for **2g** and **2j**.  The yields were determined
15    by reverse phase HPLC with Zorbax SB-Phenyl or YMC ODS-AM
columns and MeCN/0.1% H₃PO₄ as the mobile phase.


## EXAMPLE 1

20    Oxidation of Primary Alcohol—TEMPO Oxidation

$$R^1\diagup OH \quad \xrightarrow[\text{NaClO}]{\substack{\text{NaClO}_2 \\ \text{TEMPO}}} \quad R^1CO_2H$$

Formula II                                  Formula I


A mixture of the primary alcohol 1 (40 mmol) in
MeCN (200 mL) and sodium phosphate buffer (0.67 M, pH= 6.7 ) was
25    heated to 35 °C.  TEMPO (436 mg, 2.8 mmol) was added then a solution of
sodium chlorite (9.14 g 80%, 80.0 mmol in 40 mL water) and a solution of
dilute bleach (1.06 mL 5.25% bleach diluted into 20 mL, 2.0mol%) were
added simultaneously in 2 hours.*

*Do not mix the sodium chlorite solution and bleach prior to
30                    the addition since the mixture appears to be unstable.  The
addition should be carried out as follows:  approximately
20% of the sodium chlorite solution is added followed by 20%

14

of the dilute bleach. Then the rest of the NaClO₂ solution
and dilute bleach are added simultaneously in 2 hours. The
reaction is slightly exothermic.

The mixture was stirred at 35 °C until the reaction is

5    complete (<2A% SM, 2-4 h) then cooled to rt. Water (300 mL) was added
and the pH was adjusted to 8.0 with 2.0 N NaOH (~48 mL). The reaction
was quenched by pouring into cold (0 °C) Na₂SO₃ solution (12.2 g in 200
mL water) maintained < 20 °C. The pH of the aqueous layer should be
8.5-9.0 After stirring for 0.5 hour at rt, MTBE (200 mL) was added with

10   stirring. The organic layer was separated discarded. More MTBE (300
mL) was added and aqueous layer was acidified with 2.0 N HCl (~100
mL) with stirring to pH = 3-4. The organic layer was washed with water
(2 x 100 mL), brine (150 mL) to give a solution of the crude carboxylic acid
2 in 90-95% yield.

15


## EXAMPLE 2

Preparation of 2-bromo-5-methoxybenzyl alcohol



20          Sodium borohydride (8.6 g) is slurried in THF (150mL
KF=150 µg/mL) in a round bottom flask equipped with a thermocouple,
an addition funnel,  a nitrogen inlet a mechanical stirrer and a cooling
bath. 2-Bromo-5-methoxybenzoic acid (50 g) is dissolved in THF (100mL
KF= 150 µg/mL) is added to the sodium borohydride slurry over 45 min

25   while maintaining the temperature at 20-25°C. The reaction must be
controlled with intermittent cooling and by careful monitoring of the
addition rate. The mixture is aged for 30 min at 20-25°C. Boron
trifluoride etherate (36.9 g) is added over a period of 30 min at 30-35°C.

The addition of boron trifluoride etherate produces a delayed

30   exotherm and  should be added slowly in  order to control the reaction

15

temperature.  The resulting white slurry is aged for 1 h at 30-35°C and
then sampled for HPLC assay. A peak at RT = 8.7 min is an impurity
related to the starting material.  The acid is at RT = 9.1min.

The reaction mixture is cooled to 15°C and carefully
5    quenched into a cold (10 °C) saturated ammonium chloride solution (150
mL) while maintaining the temperature < 25°C.

Ethyl acetate (500 mL) is added and the layers are
separated. The organic layer is washed with water (100 mL) and then
transfered to a 1L round bottom flask equipped for distillation. The
10   solution was concentrated and charged with fresh ethyl acetate. This is
repeated until a solution with a volume of 200 mL has KF<200
μg/mL.The solvent is then switched to DMF to give the final volume of
200 mL  with a KF<200 μg/mL.

15                              EXAMPLE 3
Preparation of 2-bromo-5-methoxybenzyl chloride
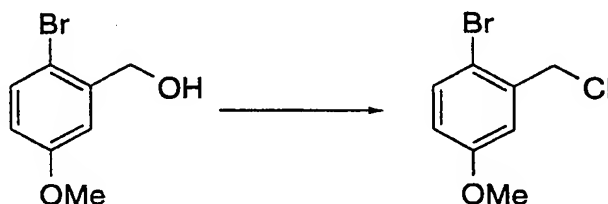


20           The DMF solution of the benzyl alcohol (91.3 g  in 400mL
KF=300 μg/mL) is charged to a 2 L flask equipped with a mechanical
stirrer, thermocouple, $N_2$ inlet, and cooling bath. The solution is cooled
to 0-5°C and the addition funnel is charged with thionyl chloride (55.0 g).
The thionyl chloride is added over a period of 45 min  while maintaining
25   the temperture 5-10°C.  The mixture is aged for 1 h at 5°C and assayed by
HPLC.

The addition funnel is charged with water (400 mL) which
is added dropwise to the reaction mixture over a period of 30 min. while
maintaining the temperture < 15°C.  The temperature is controlled by

cooling and monitoring the rate of addition. The initial addition of water
is highly exothermic. Using large excess of thionyl chloride results in a
more exothermic quench.  If the quench temperture is not controlled,
hydrolysis of the benzyl chloride back to the alcohol may result.

5          The resulting thick  white slurry is aged for 1 h at  0-5°C.
The benzyl chloride is isolated by filtration. The cake is washed with
(1:1) DMF:H$_2$O (100mL) and then water (200 mL). The solid is dried in
vacuo  to give 93 g of the benzyl chloride( 94% yield, 96 A%).
HPLC assay: Column: Waters Symmetry C8, 4.6 x 250mm; UV

10   Detection: 220 nm; Column Temp: 25 °C; Flow rate: 1 mL / min.; Eluent:
CH$_3$CN:H$_2$O:0.1% H$_3$PO$_4$  (70:30); RT (benzyl alcohol) = 3.9 min; RT
(benzyl chloride) = 7.3 min.; and RT (DMF) = 2.6 min.


## EXAMPLE 4

15   Preparation of the Acetonide of N-propanoyl (1R,2S)-cis-aminoindanol
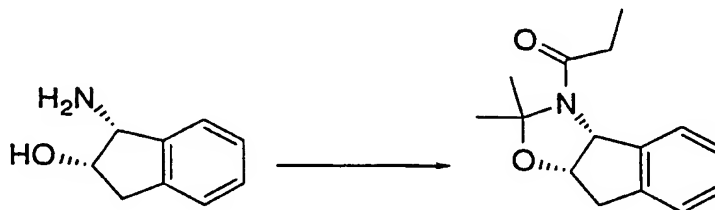


A 5 L 3-neck round bottom flask equipped with a
mechanical stirrer, N$_2$ inlet, thermocouple probe, heating mantle, and
20   addition funnel is charged with (1R,2S)-cis-aminoindanol (100 g),
tetrahydrofuran (1.2 L, KF 120 µg/mL), and triethylamine (96 mL, KF
500 µg/mL). The resulting slurry is heated under a N$_2$ atmosphere to 40-
45°C giving a yellow solution. Propionyl chloride (59 mL) is charged to an
addition funnel and added to the solution while maintaining the
25   temperature at  45-50°C.

The temperature is controlled by rate of propionyl chloride
addition and a cooling bath. HPLC assay shows >99% amide formed.
Methanesulfonic acid (3 mL) is added to the reaction slurry. 2-

Methoxypropene (140 mL) is charged to an addition funnel and added over 30 minutes at a temperature of 50°C.

The addition of 2-methoxypropene is mildly exothermic. The temperature is maintained by the rate of addition and a heating mantle. The reaction remains a slurry but does become less thick.

The reaction slurry is aged for 1-2 hours at 50°C. HPLC assay at this point shows <0.5A% of the amide remaining. The amide is not removed in the isolation so it is important to push the reaction to completion. The reaction slurry is cooled to 0-5°C and quenched by addition of 5% aqueous sodium carbonate solution (1 L) and heptane (1 L). The layers are stirred and separated and the organic is washed with water (300 mL).

HPLC assay at this point shows the acetonide in >98A% and >90% yield. The acetonide/THF/heptane solution is filtered into a 2 L round bottom flask and the solution is distilled to a final volume of 700mL. Heptane (1L) is added and the solution is distilled to a final volume of 700mL. The distillation is done under partial vacuum at ~50°C. NMR assay at this point shows < 2 mol% THF. The solution is allowed to cool and is seeded with acetonide at 35-40°C. The thick slurry is aged for 1 hour at ambient temperature then cooled to 0-5°C and aged for 1 hour. The slurry is filtered and the cake is washed with cold heptane (200 mL) and air dried to yield acetonide as a crystalline white solid (141.1 g, 85% yield, 99.6 A%).

## EXAMPLE 5

Alkylation of the Acetonide with 2-bromo-5-methoxybenzyl chloride.
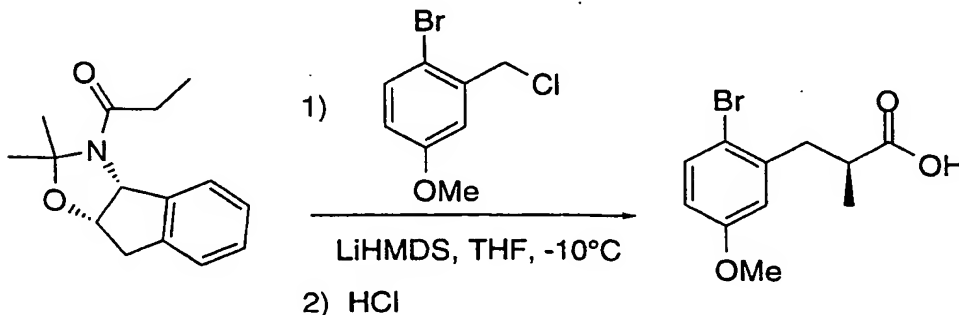
A THF solution (2L, KF< 200 µg/mL) of the acetonide (252 g) and the benzyl chloride (255 g) is cooled to -10°C. Lithium bis(trimethylsilyl)amide (1.45 L) is added dropwise over 5 h at 0-2°C. The mixture is then aged for 1.5 h and assayed by HPLC.

5      The reaction is quenched by adding aqueous saturated ammonium chloride solution (1 L). The initial addition of the ammonium chloride should be slow in order to control the foaming. The rate can be increased when the foaming subsides.

The quenched reaction is then transfered into a mixture of
10    aqueous ammonium chloride (1.5 L), water (0.5 L), and ethyl acetate (3 L). The mixture is then agitated for 15 min and the layers are separated. The organic layer is washed with water (1 L) and brine (0.5 L). The ethyl acetate solution is concentrated to a low volume and solvent switched to 1,4-dioxane. The dioxane solution is adjusted to a final volume of 1.8 L.

15    The dioxane solution of the coupled product is charged to a 12 L round bottom flask and 6 M HCl (1.5 L) is charged. The mixture is heated to reflux and monitored by HPLC.

The mixture is cooled to 20°C and MTBE (3 L) is added. The mixture is agitated for 15 min and the layers are separated. The organic
20    layer is washed with water (1 L). The MTBE solution of the crude acid is extracted with 0.6 M sodium hydroxide (2 L). The aqueous solution of the sodium salt of the acid is combined with MTBE (2.5 L) and cooled to 10°C.

The two phase mixture is acidified with 5.4 M sulfuric acid (250 mL), agitated for 15 min, settled and the layers separated. The
25    MTBE solution of the acid is washed with water (0.5 L). The MTBE solution of the acid is dried by distillation and then solvent switched to THF. The final volume of the THF is 2 L with a KF < 250 µg/mL.
HPLC assay: column: Waters Symmetry; Eluent: acetontrile: water: phosphoric acid (70:30:0.1); Flow rate: 1 mL/min.; RT (acetonide)= 4.5
30    min.; RT (benzyl chloride) = 7.5 min.; RT (coupled product) = 11.5 min.; RT (aminondanol) = 1.7 min.; RT (hydroxyamide) = 1.7 min.; and RT (acid) = 4.5 min.

## EXAMPLE 6

Preparation of 3-(2-bromo-5-methoxyphenyl)-2-methylpropanol
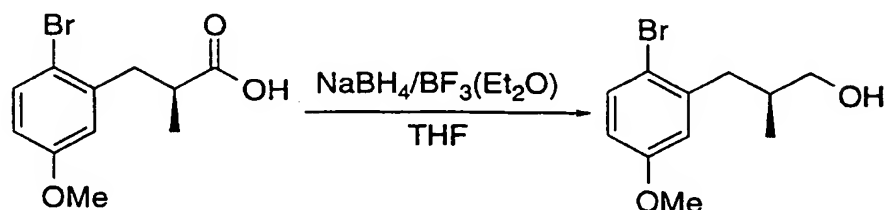


Sodium borohydride (33 g) is slurried in THF (0.5 L KF=200
5    μg/mL) in a round bottom flask. The THF solution (2 L) of the acid is
added to the sodium borohydride slurry over 1 h while maintaining the
temperature at 20-25°C.

The reaction is controlled with a cooling bath and by
carefully monitoring the addition rate. A nitrogen sweep and proper
10   venting of the hydrogen is also important.

The mixture is aged for 30 min at 20-25 °C. Boron trifluoride
etherate (152 g) is added over 1 h at 30-35 °C. The addition produces a
delayed exotherm and should be carefully monitored in order to control
the reaction temperature. The resulting milky white slurry is aged for 1
15   h at 30 °C and sampled for HPLC assay.

The reaction mixture is cooled to 15 °C and carefully
quenched in a cold (10°C) ammonium chloride solution (1.5 L) while
maintaing the temperature at 25 °C. The rate of hydrogen evolution is
controlled by the rate of the addition of the mixture into the ammonium
20   chloride. The quenched mixture is distilled *in vacuo* to remove the
THF. The aqueous layer is extracted with MTBE (1.5 L) and the organic
layer is dried by flushing with additional MTBE. The MTBE solution is
then solvent switched to hexanes and adjusted to a volume of 350 mL and
seeded. The slurry is aged for 2 h at 20 °C and then cooled to 0-5 °C aged
25   for 1 h and filtered. The cake is washed with cold hexanes (200 mL). The
solid is dried under a nitrogen sweep. The isolated solid (164 g) is >
99A% by HPLC and > 99%ee.

## EXAMPLE 7

Preparation of 3-(2-bromo-5-methoxyphenyl)-2-methylpropanoic acid
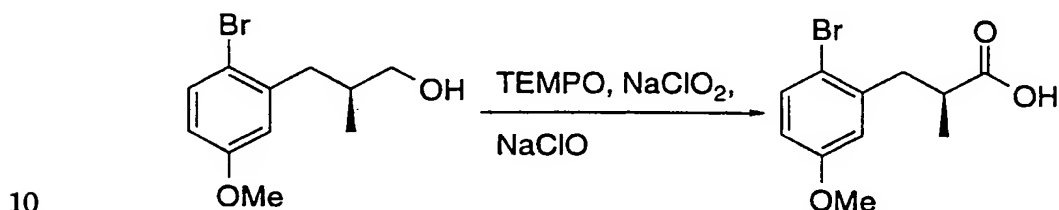


The acid was prepared following the general procedure recited in Example 1.

**2g:** $^1$H NMR (CDCl$_3$) δ: 7.44 (d, J=8.7 Hz, 1H), 6.78 (d, J=3.1 Hz, 1H), 6.66 (dd, J=8.7, 3.1 Hz, 1H), 3.75 (s, 3H), 3.13 (dd, J=13.1, 6.8 Hz, 1H), 2.98-2.84 (m, 1H), 2.77 (dd, J=13.1, 7.4 Hz, 1H), 1.23 (d, J=6.9 Hz, 3H).

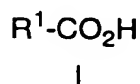**2j:** $^1$H NMR (CDCl$_3$) δ: 9.0–8.0 (broad, 1 H), 7.47–7.30 (m, 5H), 5.71 (d, J = 7.7 Hz, 1H), 4.43 (d, J = 7.7 Hz, 1H), 2.70-2.40 (m, 2H), 2.33–2.27 (m, 1H), 2.17–1.80 (m, 3H), 1.58 (s, 3H).

$^{13}$C NMR (CDCl$_3$) δ: 172.04, 169.48, 137.52, 128.73, 126.16, 94.66, 77.05, 64.34, 34.52, 29.91, 23.45, 17.28.

Anal. Calcd for C$_{15}$H$_{17}$NO$_4$: C, 65.44; H, 6.22; N, 5.09. Found C, 65.31; H, 6.15; N, 4.98.

WHAT IS CLAIMED IS:

1.    A process for preparing a compound of Formula I:

$$R^1\text{-}CO_2H$$

I

wherein:

$R^1$ is:

a)    H,

b)    $C_1\text{-}C_8$ alkyl,

c)    $C_2\text{-}C_8$ alkynyl,

d)    $C_3\text{-}C_7$ cycloalkyl,

e)    aryl,

f)    heteroaryl, or

g)    heterocyclyl;

$C_1\text{-}C_8$ alkoxy, $C_1\text{-}C_8$ alkyl, $C_2\text{-}C_8$ alkynyl, or $C_3\text{-}C_8$ cycloalkyl, are unsubstituted or substituted with one, two or three substituents selected from the group consisting of: OH, $CO_2R^4$, Br, Cl, F, I, $CF_3$, $C_1\text{-}C_8$ alkoxy, $C_3\text{-}C_8$ cycloalkyl, aryl, heteroaryl, heterocyclyl, and $CO(CH_2)_nCH_3$,

aryl is defined as phenyl or naphthyl , which is unsubstituted or substituted with one, two or three substituents selected from the group consisting of: OH, $CO_2R^4$, Br, Cl, F, I, $CF_3$, $C_1\text{-}C_8$ alkoxy, $C_1\text{-}C_8$ alkyl, $C_2\text{-}C_8$ alkynyl, or $C_3\text{-}C_8$ cycloalkyl, $CO(CH_2)_nCH_3$, or when aryl is substituted on adjacent carbons they can form a 5- or 6-membered fused ring having one, two or three heteroatoms selected from O, N, and S, this ring is unsubstituted or substituted on carbon or nitrogen with one, two or three substituents selected from the group consisting of: OH, $CO_2R^4$, Br, Cl, F, I, $CF_3$, $C_1\text{-}C_8$ alkoxy, $C_1\text{-}C_8$ alkyl, $C_2\text{-}C_8$ alkenyl, $C_2\text{-}C_8$ alkynyl, $C_3\text{-}C_8$ cycloalkyl, and $CO(CH_2)_nCH_3$;

heteroaryl is defined as a 5- or 6-membered aromatic ring containing 1, 2 or 3 heteroatoms selected from O, N and S ,

which is unsubstituted or substituted with one, two or three substituents selected from the group consisting of: OH, $CO_2R^4$, Br, Cl, F, I, $CF_3$, $C_1$-$C_8$ alkoxy, $C_1$-$C_8$ alkyl, $C_2$-$C_8$ alkynyl, $C_3$-$C_8$ cycloalkyl, $CO(CH_2)_nCH_3$, and additionally —

5        the 5- or 6-membered aromatic ring can be benzofused and unsubstituted or substituted with one, two or three substituents as described above;

heterocyclyl is defined as a 5- or 6-membered, non-aromatic ring containing 1, 2 or 3 heteroatoms selected from O, N and S,

10        which may contain one or two double bonds and which is unsubstituted or substituted with one, two or three substituents selected from the group consisting of: OH, $CO_2R^4$, Br, Cl, F, I, $CF_3$, $C_1$-$C_8$ alkoxy, $C_1$-$C_8$ alkyl, $C_2$-$C_8$ alkynyl, $C_3$-$C_8$ cycloalkyl, $CO(CH_2)_nCH_3$, and additionally

15        the 5- or 6-membered ring can be benzofused and unsubstituted or substituted with one, two or three substituents as described above;

n is: 0 to 5;

20

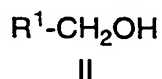t is: 0, 1 or 2;

$R^4$ is: H, or $C_1$-$C_8$ alkyl; or

25    comprising the following steps:

     1)      adding to a compound of Formula II in a solvent,

$$R^1\text{-}CH_2OH$$

$$II$$

     a solution of phosphate buffer to maintain a pH of about 4.0 to about 8.0;

30

     2)      maintaining the phosphate-buffered biphasic mixture of the compound of Formula II at about 0°C to about 50°C;

3) adding a catalytic amount of TEMPO to the mixture; and

4) charging the TEMPO/phosphate-buffered biphasic mixture —
   with a solution of sodium chlorite and a catalytic amount of
   sodium hypochlorite to oxidize to the compound of Formula I.

2. The process as recited in Claim 1, wherein the
solvent is selected from the group consisting of: acetonitrile,
tetrahydrofuran, diethyl ether, MTBE (methyl t-butyl ether), DME
(dimethoxyethane), DIGLYME (2-methoxyethyl ether), TRIGLYME
(triethylene glycol dimethyl ether), toluene, benzene, hexane, pentane,
dioxane, or a mixture of said solvents, including a mixture of said
solvents with water.

3. The process as recited in Claim 2, wherein the
phosphate buffer comprises an aqueous mixture of NaOH, KOH,
$NaH_2PO_4$, $KH_2PO_4$, $Na_2HPO_4$, and $K_2HPO_4$, sufficient to maintain a pH of
about 4.0 to about 8.0.

4. The process as recited in Claim 3, wherein TEMPO
(2,2,6,6-tetramethyl-1-piperidinyloxy, free radical) is used in about 1.0 to
about 10.0 mole percent.

5. The process as recited in Claim 4, wherein sodium
chlorite is used in about 1.0 to about 3.0 equivalents.

6. The process as recited in Claim 5, wherein sodium
hypochlorite is used in about 1.0 to about 7.0 mole percent.

7. The process as recited in Claim 6, wherein the
reaction temperature is about 0°C to about 50°C.

8. The process as recited in Claim 7, wherein the
phosphate buffer comprises an aqueous mixtureof NaOH, KOH,

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NaH$_2$PO$_4$, KH$_2$PO$_4$, Na$_2$HPO$_4$, and K$_2$HPO$_4$, sufficient to maintain a pH of about 6.5 to about 7.0.

5        9.     The process as recited Claim 8, wherein TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy, free radical) is used in about 5.0 to about 7.0 mole percent.

       10.    The process as recited in Claim 9, wherein sodium chlorite is used in about 2.0 equivalents relative to the compound of

10   Formula II.

       11.    The process as recited in Claim 10, wherein sodium hypochlorite is used in about 2.0 to about 5.0 mole percent.

       12.    The process as recited in Claim 11, wherein the

15   reaction temperature is about 35°C to about 40°C.

       13.    The process as recited in Claim 12, wherein the reaction time is about 2 hours to about 4 hours.

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# INTERNATIONAL SEARCH REPORT

| A. | CLASSIFICATION OF SUBJECT MATTER |
|---|---|

IPC(6)  :C07C 51/16
US CL  :562/409
According to International Patent Classification (IPC) or to both national classification and IPC

| B. | FIELDS SEARCHED |
|---|---|

Minimum documentation searched (classification system followed by classification symbols)

U.S.  :  562/409

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, CA OLD, CA PLUS
search terms: CA Reg numbers for TEMPO, NaClO2, NaClO

| C. | DOCUMENTS CONSIDERED TO BE RELEVANT |
|---|---|

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | NOOY, A.E.J. et al. On the use of stable organic radicals for the oxidation of primary and secondary alcohols. synthesis. October 1996, pages 1153-1174, especially pages 1161-1164. | 1-13 |
| Y | US 5,631,366 A (LOHRI et al) 20 May 1997, col 3 line 13 - col 4 line 55. | 1-13 |
| Y | ANELLI, P.L. et al. Fast and selective oxidation of primary alcohols of aldehydes or to carboxylic acids and of secondary alcohols to ketones mediated by oxoammonium salts under two-phase conditions. J. Org. Chem. 1987, Vol. 52, No. 12, pages 2559-2562, especially page 2562. | 1-13 |

| [X] | Further documents are listed in the continuation of Box C. | [ ] | See patent family annex. |
|---|---|---|---|

| * | Special categories of cited documents: | "T" | later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention |
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| "A" | document defining the general state of the art which is not considered to be of particular relevance | "X" | document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone |
| "E" | earlier document published on or after the international filing date | | |
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| "O" | document referring to an oral disclosure, use, exhibition or other means | | |
| "P" | document published prior to the international filing date but later than the priority date claimed | "&" | document member of the same patent family |

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 15 JUNE 1999 | 26 JUL 1999 |

| Name and mailing address of the ISA/US<br>Commissioner of Patents and Trademarks<br>Box PCT<br>Washington, D.C. 20231 | Authorized officer<br>ROBERT DEEMIE |
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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| Y | DALCANALE, E. Selective oxidation of aldehydes to carboxylic acids with sodium chlorite-hydrogen peroxide. J. Org. Chem. 1986, Vol. 51, No. 4, pages 567-571, see entire document. | 1-13 |